**Supplementary Material**

**Table S1. Rationale for inclusion and exclusion criteria**

**Table S2. International Classification of Disease, 9th edition, Clinical Modification (ICD-9-CM) codes used to define study clinical outcomes**

**Table S3. Model fit statistics**

**Table S4. Diagnostics of assignment accuracy**

**Table S5. Factors Associated with Suboptimal Control**

**Table S1. Rationale for inclusion and exclusion criteria**

|  |  |
| --- | --- |
| **Inclusion criterion** | **Rationale** |
| 1) Patients that remained alive throughout the year | To ensure at least one year of follow-up for every patient (in fact, we required one month for initial dose adjustment + one year of follow-up) |
| 2) Patients with at least 4 determinations of INR between months 2 and 13 after the index date (with fewer than 90 days between the index date and the first INR determination available), | To ensure a minimum level of INR monitoring throughout the year. |
| 3) Patients with gaps between determinations of less than 90 days between months 2 and 13 (or between the last INR determination available and the end of the assessment period). | To ensure a minimum level of INR monitoring throughout the year. |
| **Exclusion criterion** | **Rationale** |
| 1) Non-naïve users | Adequate design to assess outcomes.1  |
| 2) Patients who did not refill their prescription | To conform a homogeneous risk cohort. |
| 3) Patients treated for other conditions | To conform a homogeneous risk cohort. |
| 4) Patients younger than 40 years old | To conform a homogeneous risk cohort. |
| 5) Patients with valvular heart disease | To conform a homogeneous risk cohort. |
| 6) Patients without INR or incorrect INR information | Adequate INR information was not retrievable from some of the 24 Health Departments (HDs) of the VHS. We selected only HDs with INR information for at least 70% of patients in treatment. |
| 7) Patients with less than 395 days of follow-up | Minimum follow-up time required for analysis (one month for dose adjustment + one year for follow-up) |
| 8) People without health coverage by the VHS, mainly some government employees whose prescriptions are reimbursed by civil service insurers and are thus not included in the pharmacy databases of the VHS | Follow-up is limited or not possible. |
| 9) People not registered in the census (non-residents or temporary residents) | Follow-up is limited or not possible. |
| 10) People who left the region or were disenrolled from VHS coverage for other causes | Follow-up is limited or not possible. |

1. Johnson ES, Bartman BA, Briesacher BA, Fleming NS, Gerhard T, Kornegay CJ, Nourjah P, Sauer B, Schumock GT, Sedrakyan A, Stürmer T, West SL, Schneeweiss S. The incident user design in comparative effectiveness research. Pharmacoepidemiol Drug Saf. 2013 Jan;22(1):1-6

| **Table S2. International Classification of Disease, 9th edition, Clinical Modification (ICD-9-CM) codes used to define study clinical outcomes.** |
| --- |
| ***Clinical Outcomes*** |
| Isquemic stroke | 433.x1, 434.x1, 436.xx |
| TIA | 435.xx |
| GI bleeding | 455.2, 455.5, 455.8, 456.0, 456.20, 459.0,530.7, 530.82, 531.00, 531.01, 531.20, 531.21, 531.40, 531.41, 531.60, 531.61, 533.00, 533.01, 533.20, 533.21, 533.40, 533.41, 533.61, 534.00, 534.01, 534.20, 534.21, 534.40, 534.41, 534.61, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.0, 578.1, 578.9 |
| Major GI bleeding | GI bleeding + ICD-9 procedure code of blood or blood components transfusion (99.03, 99.04, 99.05, 99.06, 99.07, 99.09) |
| Intracranial haemorrhage | 430.xx, 431.xx, 432.xx, 852.0x, 852.2x, 852.4x, 853.0x |

**Table S3. Model fit statistics**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Model  | BIC | AIC | Entropy  | Minimum size |
| 2 groups | -115687.56 | -115582.71 | 0.90 | 0.40 |
| 3 groups | -113422.63 | -113219.91 | 0.86 | 0.26 |
| **4 groups** | **-112734.45** | **-112433.87** | **0.80**  | **0.10** |
| 5 groups | -112353.32 | -111954.87 | 0.80  | 0.06 |
| 6 groups | -111765.83 | -111706.41 | 0.74  | 0.05 |
| 7 groups | -111612.05 | -111542.14 | 0.73  | 0.02 |

AIC: akaike information criterion; BIC: bayesian information criteria; In bold the models selected after fulfilling all criteria. The criteria for rejecting k class models (and, thus, selecting k-1 class models) was the presence of some of the following criteria: BIC score higher; entropy (minimum membership probability) <0.7; and minimum sample size in the range of 10%.

**Table S4. Diagnostics of assignment accuracy for the 4-group model**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Trajectory | n | AvPP | OCC | p | P  |
| 1 | 780 | 0.85 | 51.71 | 0.10 | 0.10 |
| 2 | 2799 | 0.85 | 10.37 | 0.35 | 0.34 |
| 3 | 2249 | 0.86 | 15.51 | 0.28 | 0.28 |
| 4 | 2196 | 0.80 | 10.63 | 0.27 | 0.28 |

AvPP: average posterior probability; OCC: odds of correct classification; p: proportion of study members classified in each group; P: estimated probability of classification

**Table S5. Factors Associated with Suboptimal Control**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Uncontrolled | Improving Control | Worsening Control |
| Characteristics | OR | p-value | OR | p-value | OR | p-value |
| Age 64-75 (ref:<65) | 0.81 | 0.153 | 1.17 | 0.305 | 1.08 | 0.641 |
| Age>75 (ref:<65) | 1.06 | 0.660 | **1.38** | **0.033** | 1.35 | 0.060 |
| Female | 1.07 | 0.469 | 0.86 | 0.134 | 1.03 | 0.756 |
| Europe (ref: Spain) | **1.76** | **0.038** | 0.97 | 0.926 | 1.21 | 0.535 |
| Other country (ref: Spain) | 1.52 | 0.102 | 1.04 | 0.879 | 0.88 | 0.676 |
| Income>18.000/year | **1.50** | **0.000** | 1.10 | 0.339 | **1.29** | **0.019** |
| Atrial fibrillation | 0.96 | 0.834 | 0.94 | 0.785 | 0.91 | 0.667 |
| Congestive Heart Failure | **1.72** | **0.000** | 1.32 | 0.068 | 1.25 | 0.161 |
| Hypertension | 1.09 | 0.455 | 1.09 | 0.460 | 1.02 | 0.894 |
| Diabetes | **1.25** | **0.028** | 1.00 | 0.964 | 1.14 | 0.230 |
| Liver disease | 0.77 | 0.126 | 0.71 | 0.065 | 0.71 | 0.077 |
| Renal disease | **1.41** | **0.041** | 1.15 | 0.423 | 1.16 | 0.419 |
| Previous ischemic stroke or TIA | 0.96 | 0.787 | 0.88 | 0.356 | 0.87 | 0.329 |
| Thromboembolism | 1.09 | 0.654 | 0.79 | 0.250 | 0.87 | 0.510 |
| Hemorragic stroke | 0.78 | 0.674 | 0.91 | 0.874 | 1.07 | 0.916 |
| GI bleeding | 1.01 | 0.976 | 0.86 | 0.540 | 0.70 | 0.185 |
| Other bleeding | **1.42** | **0.006** | 1.26 | 0.086 | 1.20 | 0.203 |
| Vascular disease | **1.40** | **0.017** | 1.18 | 0.269 | 1.19 | 0.259 |
| Dementia | 1.61 | 0.060 | 1.19 | 0.511 | 1.58 | 0.092 |
| Depression | **1.43** | **0.020** | **1.38** | **0.044** | 1.21 | 0.272 |
| Cancer | 1.02 | 0.896 | 0.89 | 0.435 | 1.00 | 0.976 |
| *Events during first year of treatment (13 months)* |  |  |  |  |
| GI bleeding | 3,18 | 0,158 | 1,44 | 0,684 | 2,33 | 0,340 |  |  |  |  |
| Hemorragic stroke | 2,90 | 0,760 | 3,58 | 0,738 | 2,12 | 0,829 |  |  |  |  |
| Ischemic stroke | 1,88 | 0,400 | 1,84 | 0,430 | 2,36 | 0,291 |  |  |  |  |
| TIA | 0,30 | 0,165 | 0,46 | 0,334 | 0,49 | 0,408 |  |  |  |  |
| OR: Odds Ratio; GI: Gastrointestinal; TIA: Transient Ischemic Attack |  |  |  |
| Reference category is "Optimal Control" |  |  |  |  |  |  |  |  |  |
| Statistically significant categories are marked in bold |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |